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Research Report

Telencephalic neurocircuitry and synaptic plasticity in rodent spatial learning and memory

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ABSTRACT

Spatial learning and memory in rodents represent close equivalents of human episodic declarative memory, which is especially sensitive to cerebral aging, neurodegeneration, and various neuropsychiatric disorders. Many tests and protocols are available for use in laboratory rodents, but Morris water maze and radial-arm maze remain the most widely used as well as the most valid and reliable spatial tests. Telencephalic neurocircuitry that plays functional roles in spatial learning and memory includes hippocampus, dorsal striatum and medial prefrontal cortex. Prefrontal–hippocampal circuitry comprises the major associative system in the rodent brain, and is critical for navigation in physical space, whereas interconnections between prefrontal cortex and dorsal striatum are probably more important for motivational or goal-directed aspects of spatial learning. Two major forms of synaptic plasticity, namely long-term potentiation, a lasting increase in synaptic strength between simultaneously activated neurons, and long-term depression, a decrease in synaptic strength, have been found to occur in hippocampus, dorsal striatum and medial prefrontal cortex. These and other phenomena of synaptic plasticity are probably crucial for the involvement of telencephalic neurocircuitry in spatial learning and memory. They also seem to play a role in the pathophysiology of two brain pathologies with episodic declarative memory impairments as core symptoms, namely Alzheimer's disease and schizophrenia. Further research emphasis on rodent telencephalic neurocircuitry could be relevant to more valid and reliable preclinical research on these most devastating brain disorders.

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1. Introduction

Learning is often seen as a process of behavioral change resulting from experience, which includes cognitive as well as motivational aspects. Memory, on the other hand, is the capacity to retain and recall facts, previous experiences, events, impressions, etc. (Markovitsch, 2000). Neuropsychologists classically distinguish between declarative (explicit) and non-declarative (implicit, procedural) memory. Although these terms refer to the ability to speak, both aspects of memory have been identified and modeled in animals as well. Declarative memory comprises semantic and episodic subsystems (Tulving, 1984). The latter refers to the (conscious) recollection of experiences (i.e., what, where and when), and has been found to be especially sensitive to cerebral

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List of abbreviations

aCC	anterior cingulate cortex
AD	Alzheimer's disease
AMPA	α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate
APP/PS1	amyloid precursor protein presenilin 1
CA1/3	area cornu ammonis 1/3
CaMKII	calmodulin-dependent protein kinase II
DG	dentate gyrus
DLS	dorsolateral striatum
DMS	dorsomedial striatum
DSM	diagnostic and statistical manual of mental disorders
EC	entorhinal cortex
GABA	gamma-amino butyric acid
HC	hippocampus
IL	infralimbic cortex
LTP	long-term potentiation
LTD	long-term depression
MK-801	dizocilpine
mPFC	medial prefrontal cortex
MSNs	medium spiny neurons
MWM	Morris water maze
NMDA	*N*-methyl D-aspartate
NVHL	neonatal ventral hippocampus lesion
PD	postnatal day
PFC	prefrontal cortex
PL	prelimbic cortex
RAM	radial arm maze
Zif268	zinc finger transcription factor 268

aging, neurodegeneration, and various neuropsychiatric diseases (Pause et al., 2013).

The identification of complex cognitive abilities in animals that are analogous, homologous or precursory to essentially human functions remains controversial. However, most researchers consider spatial learning and memory in rodents to be at least a close equivalent of human declarative memory abilities (see Morellini, 2013). Spatial memory generally refers to information about the spatial properties of the environment, which is crucial for an animal's ability to navigate in space, and has obvious ecological importance for heavily predated and burrowing murid species.

2. Spatial learning and memory tests in laboratory rodents

Researchers devised hundreds of arenas and protocols to investigate spatial learning and memory in laboratory rodents. However, Morris water maze (MWM) and radial-arm maze (RAM) remain the most widely used. We will briefly review these two tests below, but refer to Hodges (1996) for a thorough comparison between them.

First described by Morris in the early 1980s, MWM consists of a pool filled with opaque water with a submerged escape platform (Morris, 1984; D'Hooge and De Deyn, 2001). In order to locate the hidden platform, rodents need to associate distal environmental cues with its location. During acquisition training in the hidden-platform version of the task (see Fig. 1), most authors have used performance measures such as time required to locate the hidden-platform (i.e., escape latency), path length and velocity. However, rodents have different ways to improve their performance as a result of training, and not all of these actually involve the use of spatial reference memory (Garthe and Kempermann, 2013; Stover et al., 2012). Therefore, some authors implemented more elaborate methods to assess the use of spatial search strategies (Janus, 2004; Brody and Holtzman, 2006; Garthe et al., 2009; Garthe and Kempermann, 2013; Lo et al., 2013, Stover et al., 2012; Van der Jeugd et al., 2013). These can be segregated in spatial strategies, (non-spatial) systematic strategies and repetitive looping. During the course of training, and related to increasing accuracy and directionality, normal rodents will use spatial strategies incrementally, whereas cognitively compromised animals tend to stick to non-spatial strategies (Janus, 2004; Lo et al., 2013; Stover et al., 2012).

Many deviations of the MWM task have been described that assess different aspects of learning and memory. By providing a visible platform the animal learns to swim to a cued goal, an ability that is unrelated to place learning (although mice have been shown to acquire spatial memory during this version of the task as well). Moving the platform to an alternative position (usually the opposite quadrant), the animal has to update its spatial memory during a process called reversal learning. Furthermore, working memory can be assessed using multiple-location place-learning or delayed matching-to-sample procedures, during which the platform is moved to a new location on each training session. A final example of an interesting MWM protocol variant is extinction of spatial preference following platform removal. During such extinction protocols, inhibitory learning suppresses the behaviors that were learned during acquisition (Callaerts-Vegh et al., 2006; Vorhees and Williams, 2006; Morellini, 2013).

Spatial learning and memory can also be reliably assessed in the dry-land RAM (Olton and Samuelson, 1976). A typical RAM device consists of several arms (4–8, or more) symmetrically situated around a central chamber. The commonly used win-shift version of this task requires food-deprived animals to learn to collect rewards from baited arms as efficiently as possible. The most efficient strategy in this version of the task is obviously by visiting each arm only once. The number of revisited arms (errors), and the time required for retrieving the food are measured. Alternatively, when not all arms are baited, animals must learn to avoid entering non-baited arms (Peele and Baron, 1988). Visiting non-baited arms can then be counted as reference memory errors and revisits as working memory errors. Visual or tactile stimuli can be provided to cue animals about visited and unvisited arms (Olaman and McNaughton, 2001; Packard et al., 1989). In the win-stay version of this test, animals need to return to a previously rewarded location (McDonald and White, 1993), instead of avoiding the previously rewarded location as in

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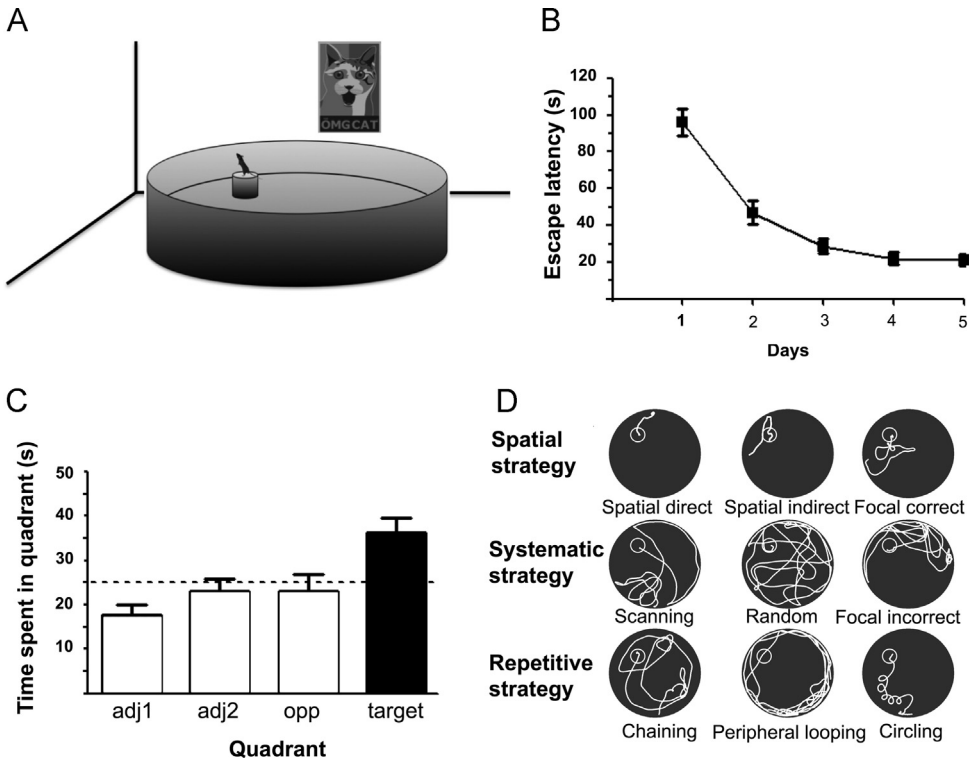

Fig. 1 – Morris water maze (MWM) and aspects of MWM performance in laboratory mice. (A) Depiction of a typical MWM set-up. In the absence of proximal cues, animals learn to navigate to the hidden escape platform using distal cues outside the pool. (B) A group of C75BL/6J mice, 6–8 weeks of age, were trained on a fixed platform position during five daily trial blocks (each consisting of 4 swim trials). The curve illustrates learning-related decrease in escape latency (time required to find the hidden platform). (C) Probe trial (100 s) performance illustrates spatial memory for the platform position as the mice spent most time searching the quadrant where the platform was located during training (target quadrant; black bar; adj, adjacent; opp, opposite). (D) Rodents may use spatial, systematic or repetitive strategies to locate the hidden platform. During hidden-platform training, normal mice tend to progress from non-spatial (systematic or repetitive) to hippocampus-dependent spatial strategies, which are more cognitively demanding.

the win-shift procedure. Also, reversal learning can be assessed in the RAM by switching previously baited arms to non-baited arms (Kay et al., 2011).

3. Involvement of telencephalic structures in spatial learning and memory

Declarative memory impairments have been historically described in patients with hippocampal damage. Hippocampus (HC) and its adjacent entorhinal (EC), perirhinal and parahippocampal cortices have been shown to play a crucial role in declarative and spatial memory abilities (Moser et al., 2008; Squire, 2009; Eichenbaum, 2013). In rodents, HC lesions impair spatial learning and memory in the MWM (Morris, 1984; Moser et al., 1993; Devan and White, 1999), as well as in RAM and other spatial tasks (Winocur, 1982; Demas et al., 1995; Paylor et al., 2001; Bevins and Besheer, 2006; Deacon and Rawlins, 2002). However, some behavioral deficits following large lesions may in fact have resulted from damage to other association areas in rodent telencephalon (Lipp and Wolfer, 1998).

Eichenbaum (2001) proposed that HC helps to record episodic memories (not merely spatial) as well as identify and link common features between these episodes. By and large, HC appears to be an associative device that integrates inputs from different sensory modalities (Van der Jeugd et al., 2009). It may be especially critical to the temporal organization of non-spatial and spatial events that comprise episodic memories (Shapiro and Eichenbaum, 1999; Eichenbaum, 2013). Simple maps can be integrated into complex maps through higher-order associative processes (Leising and Blaisdell, 2009). Notably, more abstract abilities of episodic memory and planning may have evolved from the ability to navigate in the physical world (Buzsáki and Moser, 2013).

Human prefrontal cortex (PFC) is definitely involved in episodic memory (Tulving et al., 1994; Graham and Levine, 2004), but has been proposed to be specifically essential for remembering contextual details of an experience, rather than memory formation as such (Gabrieli and Kao, 2007). Although not yet well defined, medial PFC (mPFC) appears to play a role in rodent spatial learning as well. Rodent mPFC can be subdivided in dorsal (anterior cingulate cortex, aCC) and ventral areas (prelimbic/infralimbic cortex, PL/IL), which could have different functions (Delatour and Witter, 2002; Uylings et al., 2003). PL/IL has been shown to govern memory flexibly during reversal and extinction learning (Lacroix et al., 2002; Ragozzino, 2007; McDonald et al., 2008; Lattal et al., 2003; Delgado et al., 2008; Quirck and Mueller, 2008). Furthermore,

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PL/IL areas may also be important for working memory functions (Ragozzino et al., 1998; Ragozzino and Kesner, 1998; Kesner and Ragozzino, 2003). In contrast, the role of aCC remains unclear as some authors found aCC lesions to impair spatial learning (Warburton et al., 1998), whereas others did not (Sutherland et al., 1988; Teixeira et al., 2006; St-Laurant et al., 2009). aCC may contribute to organization, planning and flexibility of behavior based on previously acquired information (Meunier and Destrade, 1997; Sutherland et al., 1988; Teixeira et al., 2006), but contrary to PL/IL lesions, aCC lesions do not impair spatial working memory in rats (Ragozzino and Kesner, 1998; Aggleton et al., 1995; Ragozzino et al., 1998).

Several studies indicated that dorsal striatum plays a critical role in spatial memory and learning performance as well. The striatum is the largest component of the basal ganglia, and can be divided in functionally distinct subareas of dorsal and ventral striatum with dorsal striatum further consisting of dorsomedial (DMS) and dorsolateral (DLS) functional areas (Kreitzer and Malenka, 2008; Pennartz et al., 2009). These striatal areas indeed appear to be differentially involved in MWM performance, as well as during other spatial tasks, such as RAM (Packard et al., 1989; McDonald and White, 1993). DMS is involved in goal-directed behavior that occurs during early learning phases and flexible place learning (Devan et al., 1996, 1999; Furtado and Mazurak, 1996; Devan and White, 1999; Yin et al., 2004, 2009; Yin and Knowlton, 2006; McDonald et al., 2008; Thorn et al., 2010; Lee et al., 2014). Animals with damage to DMS typically display delayed learning curves in the hidden-platform MWM task, a tendency to swim along the walls of the pool (thigmotaxis), lower swimming velocity as well as deficits in reversal learning (Devan et al., 1996, 1999; Devan and White, 1999; McDonald et al., 2008). By and large, DMS damage impairs spatial learning, and the flexible use of efficient goal-directed search strategies, whereas DLS damage fails to induce such impairments (Devan et al., 1999; Devan and White, 1999). This latter structure seems to play a role in implicit procedural learning (McDonald and White, 1993), and the acquisition of habitual (stimulus-response based) behaviors (Packard and Knowlton, 2002; Featherstone and McDonald, 2004; Yin et al., 2004). Habits are relatively inflexible, and their formation is slow, involving DLS late in the process of learning.

4. Telencephalic neurocircuitry in spatial learning and memory

We have seen that telencephalic structures such as HC, several areas of the mPFC, and DMS are critical for specific aspects of spatial learning and memory. Researchers argue, however, that most of the brain is involved in spatial learning some way or another, and that the brain contains different systems that collaborate in a serial or parallel fashion. Many telencephalic areas have overlapping or complementary functions, and their interaction is of equal, if not greater importance than their separate involvement.

Tracer and imaging studies demonstrated conserved reciprocal connections between telencephalic structures that have been involved in spatial learning and memory (see Fig. 2), and recent research is starting to elucidate the functional significance of these interconnections. Various cortical areas send glutamatergic projections to EC (Delatour and Witter, 2002; van Groen et al., 2003; Kesner et al., 2004), which provides the main input to the HC tri-synaptic circuitry consisting of a unidirectional loop that includes 3 synaptic areas. Eventually, axons originating from hippocampal CA1

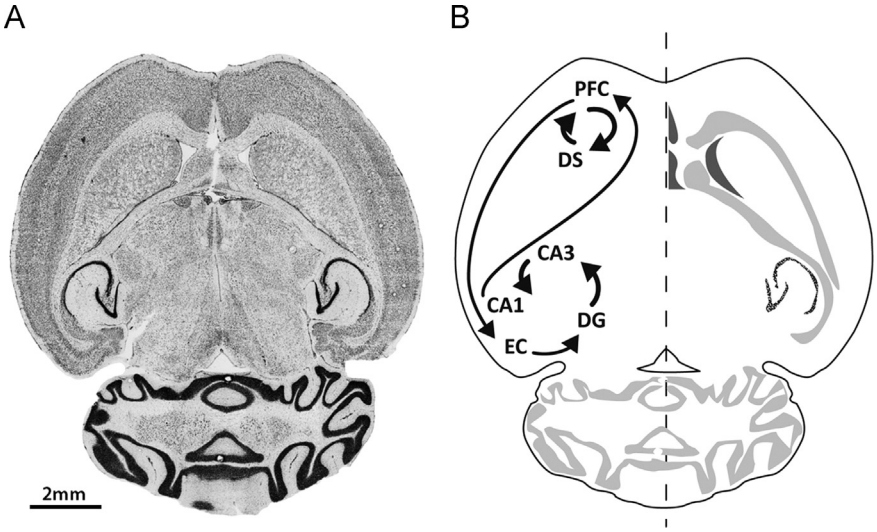

Fig. 2 – Telencephalic neurocircuitry involved in spatial learning and memory abilities. (A) Horizontal section of the mouse brain at the level of the schematic. Scale bar represents 2 mm. (B) Schematic depiction of functional relationships in the telencephalic neurocircuitry includes, first, direct and indirect PFC and HC interconnections that are critical for navigation in physical space. Mainly glutamatergic projections from cortical areas relay information to EC and henceforth to the hippocampal trisynaptic circuit (DG→CA3→CA1). Projections from CA1 to PFC mainly relay contextual and episodic information. Second, interconnections (involving other brain structures such as thalamus, not indicated in schematic) between PFC and DS are probably more important for the motivational aspects of spatial tasks. Abbreviations: DS, dorsal striatum; CA1, hippocampal CA1 area; CA3, hippocampal CA3 area; DG, dentate gyrus; EC, entorhinal cortex; PFC, prefrontal cortex.

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region project to frontal areas such as cingulate and PL cortices (Ferino et al., 1987; Jay et al., 1989; Jay and Witter, 1991; Laroche et al., 2000; Ishikawa and Nakamura, 2006; Swanson, 1981). Reciprocal connections also exist between mPFC and striatum (Di Filippo et al., 2009). DMS receives input from mPFC areas (Reep et al., 2003; Yin and Knowlton, 2006; White, 2009; Oh et al., 2014), whilst information is passed from striatum, via output nuclei of the basal ganglia (internal pallidum and substantia nigra pars reticulata) and thalamus, back to mPFC (Groenewegen et al., 1999; Heidbreder and Groenewegen, 2003).

Disconnecting HC and mPFC impairs spatial memory retrieval and planning as well as spatial working memory (Floresco et al., 1997; Wang and Cai, 2006). Spatial information appears to be acquired by HC, and transferred to mPFC in a serial fashion. In addition, disconnecting mPFC and DMS impairs performance in spatial and non-spatial tasks (Christakou et al., 2001; Dunnett et al., 2005; White and Dunnett, 2006). Some studies suggest complementary roles of mPFC and DMS (Ragozzino, 2007; McDonald et al., 2008), but the function of this system remains elusive. Using zinc finger transcription factor (zif) 268 expression patterns to map brain activity, we found that both aCC and DMS were mostly active during the early phases of MWM learning, indicating that they are important for the initial goal-directed aspects of the task (Woolley et al., 2013).

HC output may influence striatal function through its effects on cingulate cortex (Sutherland et al., 1988). Asymmetric lesions of HC and DMS result in similar effects on MWM performance to bilateral lesions, which further suggests that DMS is an intricate part of this telencephalic system (Devan and White, 1999). HC could be important for acquisition of spatial information about location of the goal, whilst DMS drives navigation towards the goal (van der Meer et al., 2010).

5. Spatial learning-related synaptic plasticity in telencephalic structures

Hebb (1949) historically postulated that associative memories are formed by a process that strengthens synaptic connections. It is now widely accepted that experience modifies behavior through activity-dependent, long-lasting synaptic modifications (Hölscher, 1999). Notably, the two major forms of synaptic plasticity, namely long-term potentiation (LTP), a lasting increase in synaptic strength between simultaneously activated neurons (Bliss and Collingridge, 1993), and long-term depression (LTD), a decrease in synaptic strength (Nakazawa et al., 2004; Citri and Malenka, 2008; Kreitzer and Malenka, 2008; Di Filippo et al., 2009), have been found to occur in HC, dorsal striatum and mPFC (Citri and Malenka, 2008; Kreitzer and Malenka, 2008; Di Filippo et al., 2009).

Both forms of synaptic plasticity involve NMDA-type glutamate receptors (Kandel et al., 2012), and calcium-dependent intracellular signaling (Bear et al., 2007). NMDA receptor-dependent increases in dendritic spine calcium concentration lead to activation of intracellular signaling cascades involving a number of protein kinases, which influence membrane conductance, AMPA receptor trafficking (Lisman and Zhabotinsky, 2001), and structural changes at the synapse (Lisman and Harris, 1993). Such synaptic plasticity is involved in the formation of stable place cell connections during spatial learning (Shapiro, 2001; Isaac et al., 2009), whereas protein synthesis is necessary to maintain changes in synaptic strength for longer periods of time (Wang and Tiedge, 2004). In addition to its function as a memory storage device, LTP may also serve as an arousal or attentional mechanism that increases non-specifically the salience of external stimuli (Shors and Matzel, 1997). A recent study using optogenetic stimulation of auditory inputs targeting the amygdala, found evidence for a causal link between these synaptic processes and memory (Nabavi et al., 2014).

Cellular mechanisms of synaptic plasticity, and their behavioral functions have been extensively studied in HC, but relatively overlooked in PFC (Martin et al., 2000; Neves et al., 2008). PFC does, however, possess the cellular machinery for synaptic plasticity, and functional roles of PFC plasticity have been suggested in animals and humans (Otani, 2003). As PFC integrates afferents from cortical and subcortical areas, synaptic plasticity could underlie learning-related changes in connectivity between PFC and other brain structures. Mechanisms of synaptic plasticity have also been implicated in learning-dependent changes in corticostriatal connectivity. Striatal GABAergic medium spiny neurons (MSNs) receive glutamatergic input from cortical areas as well as dopaminergic input from brainstem areas. Dopamine facilitates or inhibits LTP and LTD at glutamatergic synapses (Jay, 2003), and is important for information processing and the formation of long-term memory (Di Filippo et al., 2009; Kreitzer and Malenka, 2008). Notably, synaptic plasticity deficits in PFC have been implemented in various brain disorders (Goto et al., 2009).

6. Brain disorders that affect telencephalic neurocircuitry and spatial learning

Disturbances of memory functions are core pathological and diagnostic features of many brain disorders (Huber and Paulson, 1985; Förstl and Kurz, 1999; Kenworthy et al., 2008; van Os and Kapur, 2009; Pagonabarraga and Kulisevsky, 2012; Stretton and Thompson, 2012). Episodic declarative memory functions are particularly susceptible to the effects of ageing and neurodegeneration (McIntyre and Craik, 1987; Gabrieli, 1996). We will presently focus on two severe disorders of telencephalic functioning, namely Alzheimer's disease (AD) and schizophrenia, which pose major socio-medical challenges to contemporary societies.

Impaired ability to memorize new information and recall previously acquired information is a major diagnostic criterion in AD (DMS-5; American Psychiatric Association, 2013). Cognitive deficits also occur prominently in schizophrenia (Barch et al., 2013; Keefe, 2008; Tandon and Maj, 2008), but may not distinguish between schizophrenia and other psychiatric disorders (Depp et al., 2007; Reichenberg et al., 2009). However this may be, cognitive impairments remain the most therapeutically intractable psychopathological features both in AD and schizophrenia (Mangialasche et al., 2010; Karran et al., 2011; Sawa and Snyder, 2002). Psychopharmacological agents

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may even produce side effects that resemble these symptoms (Kroken et al., 2014).

Preclinical researchers hope that animal studies will further our understanding of these dramatic disorders and lead to the development of novel treatment strategies. Widely used animal models of AD- or schizophrenia-associated cognitive impairments include pharmacological and lesion approaches as well as developmental and genetic models. However, the validity of these models is still a major concern (Kaplan and Saccuzzo, 1997; Willner, 1984; Chadman et al., 2009; Homberg, 2013). In fact, none of the available models fully mimics the complex pathology of these disorders (Ashe, 2001; Floresco et al., 2005;

Table 1 – Spatial learning and (working) memory in animal models of Alzheimer's disease.

Transgene	Mutation	Age (months)	Memory process and testing procedure	Behavioral deficits	Reference
			Visual learning and memory		
APP	V7171	3–6	Morris water maze	Deficit at 3–6 mo	Moechars et al. (1999)
	Tg2576	3, 6, 9–11	Morris water maze	Intact at 3 and 6 mo, deficit at 9–11 mo	Hsiao et al. (1996)
	Tg2576	3, 9	Morris water maze	Deficit >3 mo	King et al. (1999)
			Working memory		
APP	V717F	3, 6, 9–11	Morris water maze	Deficit >6–9 mo	Chen et al. (2000)
	V717F	2, 16	T-maze: forced alternation	Intact at 2 mo, deficit at 16 mo	Chapman et al. (1999)
	V717F	3, 9	Barnes maze	Deficit >3 mo	King et al. (1999)
	V717F	11, 15	Radial arm maze	Intact at 11 mo, deficit at 15 mo	Morgan et al. (2000)
			Visual learning and memory		
Tau	P301L	2.5–9.5	Morris water maze	Intact at 2.5 mo, deficit >4 mo	Ramsden et al. (2005)
	P301L	2.5–9.6	Morris water maze	Decicit >4 mo, restoration after switch-off	Santacruz et al. (2005)
	deltaK280	10, 14	Morris water maze	Deficit >10 mo, restoration after switch-off	Sydow et al. (2011)
	P301L	3–6	Morris water maze	Deficit at 6 mo	Takeuchi et al. (2011)
	G272V and P301S	3, 6, 9	Morris water maze	Intact at 3 and 6, deficit at 9 mo	Van der Jeugd et al. (2013)
			Working memory		
	P301L	5, 7	Radial arm water maze	Intact at 5 and 7 mo	Morgan et al. (2000)
	P301S	4	Barnes maze	Intact at 4 mo	Takeuchi et al. (2011)
	P301S	3	Y-maze: spontaneous alternation	Deficit at 3 mo	Takeuchi et al. (2011)
	G272V and P301S	3, 6, 9	Y-maze: forced alternation	Deficit at 9–10 mo	Van der Jeugd et al. (2013)
			Visual learning and memory		
Other	APP/PS1(A246E)	3, 11	Morris water maze	Intact at 3 mo, deficit >11 mo	Puoliväli et al. (2002)
	APP/PS1(M146L)	3,6	Morris water maze	intact at 3, deficit >6 mo	Trinchese et al. (2004)
	APP/PS1dE9	3, 10, 15	Morris water maze	Intact at 3 mo, deficit >10 mo	Minkeviciene et al. (2008)
	APP/PS1(M146V)/ P301L	2–18	Morris water maze	Intact at 2 mo, deficit>4 mo	Billings et al. (2005)
	5xFAD (3xAPP/ 2PSEN1)	4	Morris water maze	Deficit at 4 mo, other ages not tested	Ohno et al. (2006)
			Working memory		
	Tg2576/P301L	5, 7	Radial arm water maze	Intact at 5 and 7 mo	Morgan et al. (2000)
	APP/PS1(A246E)	3, 6, 9, 12	Y-maze: spontaneous alternation	Intact at 3 mo, deficit >6 mo	Filali et al., 2009
	APP/PS1(L166P)	5, 8	Radial arm maze	Intact at 5 mo, deficit at 8 mo	Radde et al. (2006)
	5xFAD (3xAPP/ 2PSEN1)	2, 4	Y-maze: spontaneous alternation	Intact at 2 mo, deficit >4 mo	Ohno et al. (2004)

Abbreviations: AD, APP, PS1/2, Aβ.

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Neill et al., 2010; Spires-Jones and Knafo, 2012; Pozueta et al., 2013). Development of transgenic mouse models did increase our understanding of the pathogenic mechanisms of AD, but has its limitations. Similarly, selection, execution and interpretation of behavioral tests in such AD models have been exceedingly difficult (van der Staay, 2006; Schellinck et al., 2010).

7. Spatial learning and synaptic plasticity in AD models

AD is characterized by cortical atrophy, synaptic loss and neuronal cell death, neuro-inflammation, and the accumulation of amyloid plaques and tau protein-based neurofibrillary tangles (Holtzman et al., 2011). Since AD patients display progressive cognitive decline, attributed to loss of synapses and neurons in HC and other telencephalic structures, valid animal models should reproduce such deficits. MWM consequently became the golden standard test in AD mouse models. Table 1 summarizes functional impairments seen in some of the available mouse models (Ashe, 2001; Phinney et al., 2003; Götz and Ittner, 2008; Spires-Jones and Knafo, 2012; Tanila, 2012; Pozueta et al., 2013; Webster et al., 2014).

Moechars et al. (1999) reported MWM defects in 3- to 6-month-old mice expressing either mutated or wild-type amyloid precursor protein (APP), whereas Tg2576 mice that also overexpress mutant APP displayed cognitive impairment as early as 3 months (Hsiao et al., 1996; Chapman et al., 1999; King et al., 1999; Morgan et al., 2000). Many other AD models displayed defects in MWM and RAM learning that were often age dependent and robust, and could be used in preclinical studies (Chen et al., 2000; Janus et al., 2001; Brody and Holtzman, 2006).

Similar defects in spatial learning and memory have been found in several pathological tau-based AD mouse models (Pennanen et al., 2006; Götz et al., 2007; Denk and Wade-Martins, 2009; Takeuchi et al., 2011). Mouse models with inducible tau expression controlled by the CaMKII promoter develop MWM learning deficits around 10 months (Ramsden et al., 2005; SantaCruz et al., 2005; Sydow et al., 2011). An analogous impact of pathological tau on learning and memory has been observed for the full-length tau variant (Van der Jeugd et al., 2013). We also observed age-dependent learning and memory deficits in 9-month-old THY-Tau22 mice (Van der Jeugd et al., 2011, 2013). In addition, models with both amyloid and tau pathology display a comparable age-dependent cognitive decline of spatial memory capacities (Puoliväli et al., 2002; Trinchese et al., 2004; Radde et al., 2006; Minkeviciene et al., 2008; Billings et al., 2005; Ohno et al., 2004, 2006).

Models with telencephalic amyloid deposition often displayed synaptic as well as behavioral defects (Selkoe, 2002; Gengler et al., 2010), but the effects of tau mutations on synaptic functions received significantly less attention (reviewed in Spires-Jones and Knafo, 2012; Pozueta et al., 2013). Notably, Lo et al. (2013) reported impaired frontal LTP in amyloid transgenic mice, whereas frontal LTP was normal in tau transgenic mice. Several amyloid pathology models displayed deficits in hippocampal LTP, although not often at the same age, nor always clearly related to the concomitant learning and memory impairments (Chapman et al., 1999; Larson et al., 1999; Moechars et al., 1999). Some of these studies demonstrated dissociations between basal HC transmission and LTP recordings (Chapman et al., 1999; Hsia et al., 1999; Fitzjohn et al., 2001), and inconsistencies were also observed in the double transgenic APP/PS1 model displaying either reduced or normal hippocampal LTP (Volianskis et al., 2010; Fitzjohn et al., 2010), which could be related to the type of PS1 mutation. Also, telencephalic injection or infusion of oligomeric Aβ species induced alterations in HC plasticity and cognitive functions (Walsh et al., 2002; Barry et al., 2011; Cleary et al., 2005). Aβ dimers isolated directly from AD brains impaired synaptic plasticity and memory as well (Shankar et al., 2008).

Finally, transgenic mice expressing the mutated tau gene often showed altered synaptic plasticity, which coincided with spatial learning defects (Rosenmann et al., 2008; Boekhoorn et al., 2006; Chong et al., 2011; Levenga et al., 2013; Polydoro et al., 2009). However, the relationship between these functional changes is not very obvious, and several tau models displayed enhanced LTP, the significance of which is still a matter of debate. We found that pathological tau aggregation and hyperphosphorylation, leading to synaptic and neuronal loss, did actually correlate with MWM deficits, impaired hippocampal LTP and attenuated late-phase LTD (Sydow et al., 2011; Van der Jeugd et al., 2011, 2012).

8. Spatial learning and synaptic plasticity in schizophrenia models

Schizophrenia patients display pathognomonic positive and negative symptoms as well as cognitive deficits (Simpson et al., 2010). Cognitive defects best predict functional outcome in these patients (Green et al., 2004; Harvey et al., 2004), but remain mostly intractable with the available therapeutics (Papaleo et al., 2012). Visual learning and memory are one of 7 cognitive domains that are affected in schizophrenia (Green et al., 2004). Valid schizophrenia models should definitely mimic at least one of these cognitive deficits, but spatial learning and memory abilities most readily translate between animal models and humans (Hagan and Jones, 2005). However, few models have been evaluated with regard to spatial learning and (working) memory, and synaptic plasticity has been examined in even fewer models (Table 2).

The NVHL model is one of the best-characterized rodent models of schizophrenia (Lipska et al., 1993), which mimics the perinatal HC abnormalities that have been observed in schizophrenia patients. NVHL rats typically show impaired spatial learning and working memory in various protocols (Lipska et al., 2002; Chambers et al., 1996; Levin and Christopher, 2006), including the hidden-platform version of the MWM (Le Pen et al., 2000). Comparable results were found in NVHL mice that also show impaired spatial working memory, but MWM defects were rather more subtle (Naert et al., 2013).

Some pharmacological models involve blockade of NMDA receptors. For example, MK-801 is a non-competitive NMDA-receptor antagonist that induces some schizophrenia-like behaviors as well as impairs different forms of spatial learning and memory. More specifically, MK-801 has been shown to impair acquisition, reversal and working memory performance in the hidden-platform MWM task (Gorter and de Bruin, 1992; van der

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Table 2 – Spatial learning and (working) memory in animal models of schizophrenia.

Animal model	Memory process and testing procedure	Strain	Manipulation	Age testing	Behavioral deficits		Reference
NVHL	Working memory						
	T-maze: Delayed Alternation	Sprague-Dawley Rats	Excitotoxic lesion (PD7)	9 Weeks	x	Increased duration to learn the task	Lipska et al. (2002)
		Sprague-Dawley Rats	Excitotoxic lesion (8 weeks)	14 Weeks	-	Intact working memory	Lipska et al. (2002)
		C57Bl/6J Mice	Electrolytic lesion (PD6)	24 Weeks	x	Decreased time in novel arm	Naert et al. (2013)
	Y-maze: spontaneous alternation	C57Bl/6J Mice	Electrolytic lesion (PD6)	14 Weeks	x	Decreased spontaneous alternation	Naert et al. (2013)
	Radial arm maze	Sprague-Dawley Rats	Excitotoxic lesion (PD7)	PD25	x	Decreased choice accuracy	Chambers et al. (1996)
		Sprague-Dawley Rats	Excitotoxic lesion (PD7)	PD40	x	Decreased choice accuracy	Chambers et al. (1996)
		Sprague-Dawley Rats	Excitotoxic lesion (PD7)	PD80	x	Decreased choice accuracy	Chambers et al. (1996)
		Sprague-Dawley Rats	Excitotoxic lesion (PD7)	4 Weeks	x	Decreased choice accuracy	Levin and Christopher (2006)
	Visual learning and memory						
	Morris water maze (acquisition)	Sprague-Dawley Rats	Excitotoxic lesion (PD7)	>PD25	x	Increased latency	Le Pen et al. (2000)
		C57Bl/6J Mice	Electrolytic lesion (PD6)	24 Weeks	–	Intact spatial learning	Naert et al. (2013)
	Morris water maze (reference)	C57Bl/6J Mice	Electrolytic lesion (PD6)	24 Weeks	x	No preference for target quadrant after one week of training	Naert et al. (2013)
	Changing acquired information						
	Morris water maze (extinction)	C57Bl/6J Mice	Electrolytic lesion (PD6)	24 Weeks	–	Intact extinction of place memory	Naert et al. (2013)
MK-801	**Working memory**						
	T-maze task: spontaneous alternation	Wistar Rats	0.04, 0.07, 0.10 mg/kg	–	x	Decreased spontaneous alternation ≥0.07 mg/kg	van der Staay et al. (2011)
	Morris water maze	Long-Evans Rats	0.1 mg/kg	5 Months	–	Intact working memory	Vales et al. (2006)
		Wistar Rats	0.1 mg/kg	5 Months	–	Intact working memory	Vales et al. (2006)
	Visual learning and memory						
	Morris water maze (acquisition)	Wistar Rats	0.25 mg/kg	PD120-140	x	Increased latency	Gorter and de Bruin (1992)
		Wistar Rats	0.05, 0.07, 0.10 mg/kg	–	x	Increased dose-dependent latency; performance impaired (0.10 mg/kg)	van der Staay et al. (2011)
		Long-Evans Rats	0.1, 0.2 mg/kg	3 Months	x	Increased latency	Stuchlik et al. (2004)
	Morris water maze (reference)	Wistar Rats	0.25 mg/kg	PD120-140	–	Intact reference memory	Gorter and de Bruin (1992)
		Wistar Rats	0.05, 0.07, 0.10 mg/kg	–	–	Intact reference memory	

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Table 2 (*continued*)

Animal model	Memory process and testing procedure	Strain	Manipulation	Age testing	Behavioral deficits		Reference
							van der Staay et al. (2011)
	Changing acquired information						
	Morris water maze (reversal)	Long-Evans Rats	0.05, 0.08, 0.10, 0.12, 0.15 mg/kg	–	x	Increased distance to reach the platform $\geq$0.10 mg/kg	Lobellova et al. (2013)
	Morris water maze (reference)	Long-Evans Rats	0.05, 0.08, 0.10, 0.12, 0.15 mg/kg	–	x	Decreased preference for the target quadrant $\geq$0.10 mg/kg	Lobellova et al. (2013)

Abbreviations: PD, postnatal day; x, behavioral deficit found; –, no behavioral deficit found.

Staay et al., 2011; Stuchlik et al., 2004; Lobellova et al., 2013; Vales et al., 2006). Interestingly, MK-801 displays its highest binding in HC (Wong et al., 1986), and the compound is not only associated with cognitive deficits, but also with loss of HC synaptic plasticity (Coan et al., 1987; Manahan-Vaughan et al., 2008).

9. Conclusion

Rodent spatial learning and memory reliably models human episodic declarative memory abilities. MWM and RAM are definitely the most widely used tests of spatial learning and memory in laboratory rodent. The repertoire of sensitive tools to measure cognitive and behavioral changes in preclinical models remains a crucial, but often overlooked element in preclinical research on neurodevelopmental and neurodegenerative disorders.

Telencephalic neurocircuitry that plays functional roles in rodent spatial learning and memory includes HC, DMS and mPFC. PFC–HC circuitry comprises the major associative system in the rodent brain, and is critical for navigation in physical space, whereas interconnections between PFC and DMS are probably more important for the motivational and goal-directed aspects of spatial learning. Two major forms of synaptic plasticity, namely LTP and LTD also occur in HC, DMS and mPFC. These and other phenomena of synaptic plasticity are probably crucial for the involvement of telencephalic neurocircuitry in spatial learning and memory.

Episodic declarative memory is sensitive to cerebral aging, neurodegeneration, and various neuropsychiatric disorders. Alzheimer's disease and schizophrenia are two major brain pathologies with episodic declarative memory impairments as core symptoms. The search for clinically active therapeutics against these disorders has proven to be one of the most daunting challenges in contemporary neuroscience and preclinical neuropsychopharmacology. Focus on clinically relevant features of telencephalic functioning is definitely crucial to define more reliable and valid animal models for these most devastating brain disorders.

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